Impact of diabetes on clinical and safety outcomes in acute ischemic stroke patients receiving reperfusion therapy: A meta-analysis

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Abstract

Background. Patients with diabetes are known to have worse outcomes after an acute ischemic stroke (AIS) relative to those without diabetes. However, the impact of diabetes on the outcomes after the reperfusion therapy is poorly understood.

Objectives. This study investigated prognostic accuracy of diabetes and its association with clinical and safety outcomes in AIS patients receiving intravenous thrombolysis (IVT), endovascular thrombectomy (EVT), or both.

Materials and methods. Studies were identified from PubMed, Embase and Cochrane databases, using the following inclusion criteria: (a) AIS patients receiving reperfusion therapy, (b) age ≥ 18 years, (c) hemispheric stroke, and (d) the availability of comparative data between diabetic and nondiabetic groups and relevant poststroke outcomes. Random effects modelling was used to study the association of diabetes with functional outcome at discharge and at 90 days, mortality at 90 days, recanalization status, and postreperfusion safety outcomes, including rates of symptomatic intracerebral hemorrhage (sICH) and hemorrhagic transformation (HT). Forest plots of odds ratios (ORs) were generated.

Results. Of a total cohort of 82,764 patients who received reperfusion therapy, 16,877 had diabetes. Diabetes significantly increased the odds of poor functional outcome at discharge (OR 1.310; 95% confidence interval (95% CI): [1.091; 1.574]; $p = 0.0037$) and at 90 days (OR 1.487; 95% CI: [1.335; 1.656]; $p < 0.00010$), mortality at 90 days (OR 1.709; 95% CI: [1.633; 1.788]; $p < 0.0001$), sICH (OR 1.595; 95% CI: [1.301; 1.956]; $p < 0.0001$), and HT (OR 1.276; 95% CI: [1.055; 1.543]; $p = 0.0118$).

Conclusions. Our meta-analysis demonstrates that diabetes is significantly associated with poor functional outcome, increased mortality and poor postprocedural safety outcomes, including sICH and HT.

Key words: diabetes, stroke, meta-analysis, cerebrovascular disease, reperfusion therapy

Background

Diabetes is known to be an important risk factor for stroke.[1] The advent of reperfusion treatment, intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT) offers the opportunity to significantly improve the outcomes after acute ischemic stroke (AIS).[2] Moreover, since 2015, in the era of EVT, an increasing attention has been paid to identifying patients or stratifying them based on the clinical profiles or imaging factors,[3,4] who are more likely to benefit from time-critical therapies.[5–9] As such, it is of clinical relevance to fully delineate the role of diabetes in AIS, in the setting of reperfusion therapy.[10] Diabetes is known to be associated with worse functional outcomes and mortality after AIS,[11,12] largely due to its effect on endothelial dysfunction, fibrosis and vascular remodeling.[13] Furthermore, diabetes may also influence recanalization efficacy following IVT or EVT.[14]

Objectives

This study sought to estimate the prognostic accuracy of diabetes and investigate its association with clinical outcomes in AIS patients receiving IVT, EVT and/or both, by performing a meta-analysis. Our underlying questions concerning AIS patients receiving reperfusion therapy are as follows:

1. What is the prognostic accuracy of diabetes?
2. Is diabetes associated with functional outcomes at 90 days?
3. Is diabetes associated with functional outcomes at discharge?
4. Is diabetes associated with increased mortality at 90 days?
5. Is diabetes associated with safety profile (defined in terms of symptomatic intracerebral hemorrhage (sICH)[15] or any hemorrhagic transformation (HT))?
6. Is diabetes associated with recanalization status?

Materials and methods

Literature search: Identification and selection of studies

Studies were identified from PubMed, Embase and Cochrane Central Register of Controlled Trials (CENTRAL) databases for the period between January 1, 2005, and September 2021. The search terms included: "stroke", or "ischemic stroke", or "cerebrovascular accident", or "brain ischemia", or "brain infarction", or "anterior circulation", or "middle cerebral artery (MCA) stroke", or "internal carotid artery (ICA) stroke", or "MCA occlusion", or "large vessel occlusion" and "reperfusion", or "endovascular thrombectomy", or "thrombolysis", or "thrombolytic therapy", or "tissue plasminogen activator", or "clot retrieval" and "diabetes", or "diabetes mellitus" and" clinical outcome", or "tissue outcome", or "mortality", or "morbidity", or "death", or "adverse outcome", or "NIHSS (National Institute of Health Stroke Scale/Score)", or "clinical severity", or "discharge outcome", or "infarct volume", or "disability score", or "modified Rankin Score", or "prognosis". The full search term/strategy is provided in the Online Supplementary Information (Search Strategy). Studies written in a language other than English and not including human subjects were excluded by applying additional limits. Moreover, reference lists of relevant articles, systematic reviews and meta-analyses were also searched manually in order to retrieve additional articles. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart shows the search strategy, included studies and various subgroup analyses performed in the meta-analysis (Fig. 1). The following reporting frameworks adhered to and were reported: the Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist (Supplementary Table 5), PRISMA 2020 checklist (Supplementary Table 6), and Standards for Reporting of Diagnostic Accuracy Studies (STARD) 2015 checklist (Supplementary Table 7); all available in Online Supplementary Information.

Inclusion and exclusion criteria

Studies were eligible if they met the following criteria: (a) AIS patients receiving reperfusion therapy (IVT or EVT); (b) age ≥18 years; (c) hemispheric stroke; (d) availability of comparative data between diabetic and nondiabetic groups and relevant poststroke outcome data; and (e) studies with correct methodological design (studies with sufficient sample size, determined to be ≥20 patients in each group). The exclusion criteria were as follows: 1) patients with posterior circulation stroke; 2) animal studies; 3) duplicated publications; 4) full-text of the article not available; 5) thrombolytic agent other than tissue plasminogen activator (tPA) used; 6) intra-arterial thrombolysis used; 7) systematic reviews, meta-analyses, letters, and case reports or case series; and 8) studies presented in the abstract form, with relevant data on diabetes not available or no relevant postreperfusion clinical outcome measured.

Data extraction

First, the titles and abstracts were reviewed in Endnote (Clarivate Analytics, London, UK) to rule out the articles mismatched to the eligibility criteria. The remaining articles were examined thoroughly to determine whether they should be included in the systematic review or meta-analysis, according to the eligibility criteria. The screening was conducted independently by 2 authors. The disagreements were discussed and final decisions were reached

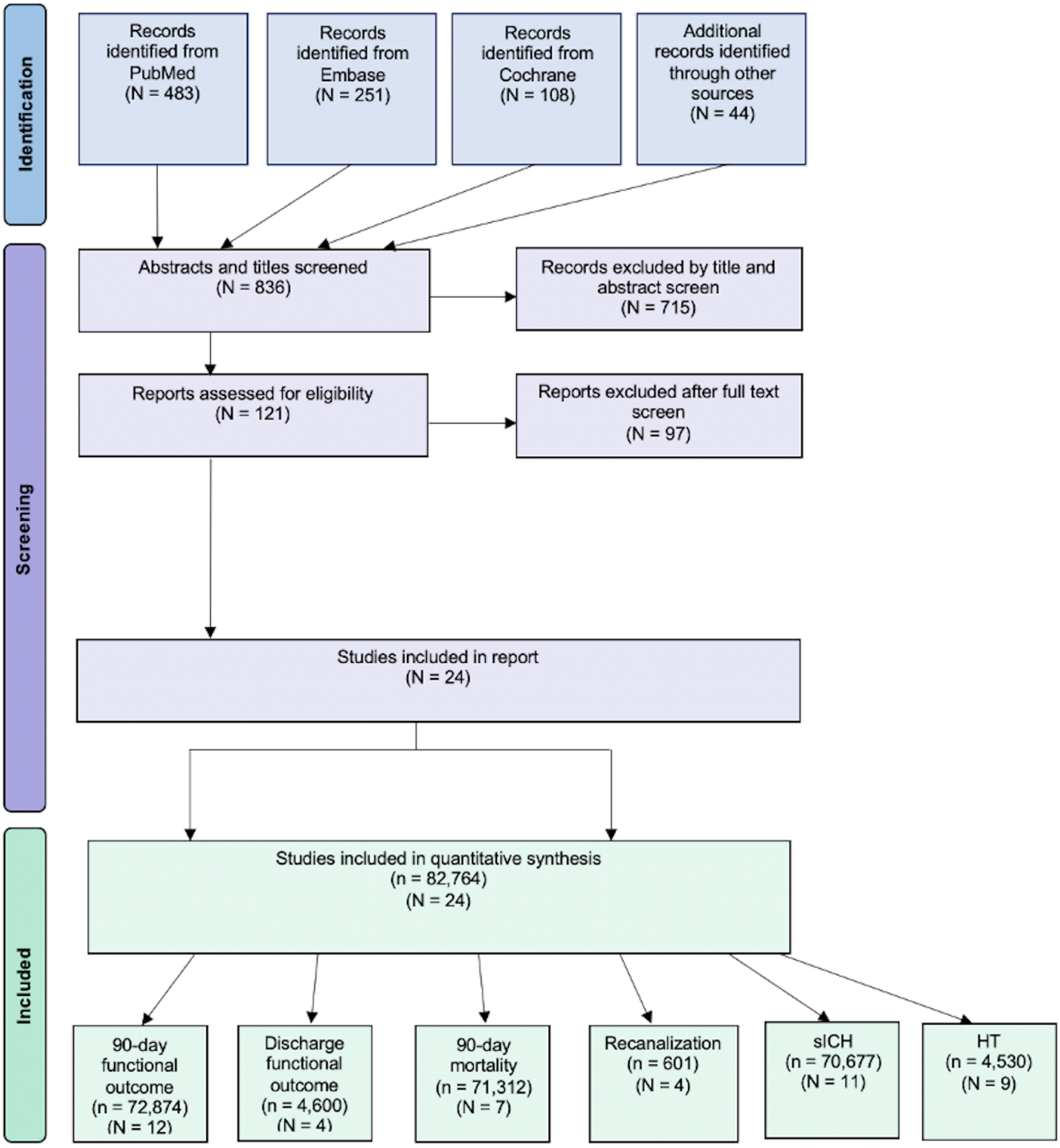

Fig. 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart showing the studies included in the meta-analysis

n – cohort size; N – number of studies; sICH – symptomatic intracerebral hemorrhage; HT – hemorrhagic transformation.

by consensus. The data from each study/trial were extracted independently using a data extraction sheet to obtain the following information: 1) baseline demographics: author, country and year of publication; 2) study population: age of patients, sample size, characteristics of acute stroke patients, presence or absence of diabetes; 3) type and time window of the treatments; and 4) outcome measures: the functional outcome at 90 days, the functional outcome at discharge, mortality at 90 days, sICH, HT, and the recanalization status. The functional outcome was measured using the modified Rankin Scale (mRS) score. The sICH was determined using Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST), the Second European-Australasian Acute Stroke Study (ECASS-II) or the Third European Cooperative Acute Stroke Study (ECASS-III) criteria, and HT was defined as any hemorrhage

observed on follow-up imaging. If a study reported more than one type of sICH, SITS-MOST results were used.

Methodological quality assessment of included studies

The methodological quality assessment using the modified Jadad analysis (MJA) scale of all studies included in the meta-analysis was performed independently by 2 researchers.[16] Moreover, the risk of bias in the results owing to funding was also evaluated, based on the declaration of funding sources and conflicts of interest obtained from individual studies.[17]

Statistical analyses

All statistical analyses were performed using STATA v. 13.0 (StataCorp, College Station, USA). The baseline characteristics of the overall cohort included in the meta-analysis were derived from all included studies. Means and standard deviations (SDs) were calculated from the medians and interquartile ranges (IQRs) using the method of Wan et al., where appropriate.[18]

The prognostic utility of diabetes was evaluated by estimating the pooled sensitivity (SENS) and specificity (SPEC), positive and negative predictive values, positive and negative likelihood ratios, and area under the curve (AUC) (a global measure of prognostic accuracy obtained from summary receiver operating characteristic (SROC) curves), by performing a meta-analysis for each prognostic outcome.[19] Moreover, the prognostic model was characterized using the goodness-of-fit test. The Deeks' funnel plot asymmetry test was used to assess the publication bias.

To examine the impact of diabetes on postreperfusion sICH and HT, functional outcomes at discharge, and functional outcomes and mortality at 90 days, a random effects meta-analysis designed by DerSimonian and Laird (DL) was used. Summary effects and heterogeneity measures obtained for each prognostic outcome from the meta-analysis were tabulated. For the odds ratios (ORs), 95% confidence intervals (95% CIs), percentage weights, and the heterogeneity across studies included in the meta-analysis, forest plots were created (Fig. 2). The heterogeneity between the studies was assessed using the I^2 statistics and p-value (<40% = low, 30–60% = moderate, 50–90% = substantial, 75–100% = considerable).[20] The random effects model was used across all subgroup analyses. The subgroup analyses for IVT or EVT studies were also performed. The presence of publication bias was visually detected using Begg's funnel plot. In the funnel plot, any asymmetry on either side indicated the presence of publication bias. We have also computed meta-analysis estimates when a specific study was excluded, to account for the influence of the individual study on the overall meta-analysis (Supplementary Fig. 5 in Online Supplementary Information). The value of $p < 0.05$ was considered statistically significant.

Results

Description of included studies

A total of 24 studies, comprising 82,764 patients, were included in this meta-analysis. Eighteen studies included patients who primarily received IVT, with or without EVT; 6 studies included patients who primarily received EVT, with or without IVT. Nine studies were excluded from this meta-analysis because they had cohort sizes that were too small, 5 were excluded for having the same cohort (or part of the same cohort) as later studies and 1 was excluded because of the use of intra-arterial thrombolysis as the treatment.

Of all patients included in this meta-analysis, 16,877 had diabetes (20.4%). The mean age ± standard deviation (SD) of all included studies was 69.5 ±33.4 years (n = 77,319). With regard to clinical history, 22.8% of patients had atrial fibrillation (n = 78,804), 37.5% had dyslipidemia (n = 74,551), 67.6% had hypertension (n = 64,064), 18.4% had prior stroke and/or transient ischemic attack (TIA) (n = 75,242), and 18.6% were prior or current smokers (n = 62,208). The description of the clinical characteristics and outcomes of the studies included in the meta-analysis can be found in Table 1 and Table 2, respectively.

Summary effects and heterogeneity from the meta-analysis on the association of diabetes are provided in Table 3. Supplementary Table 1 also provides the summary of the level of significance of the association of diabetes with various clinical and/or safety outcomes. There were variations in definitions of sICH and recanalization status across studies. The findings of the assessment of methodological quality and funding bias of the included studies are given in Supplementary Table 3. Effect size analyses for the functional outcome, sICH, HT, mortality, and recanalization status are also presented (Supplementary Fig. 6). Two studies demonstrated a moderate potential for funding bias and 1 study demonstrated a significant potential (Supplementary Table 3). The publication bias assessment, using the Egger's test, of the included studies is summarized in Supplementary Table 4. The subgroup analysis was conducted to address the prognostic (n = 24 studies) capability of diabetes in AIS.

Prognostic capability of diabetes in acute ischemic stroke

The SROC curves for diabetes to predict the outcomes are shown in Fig. 3. A summary of prognostic summary estimates is provided in Supplementary Table 2 and Supplementary Fig. 3. Supplementary Fig. 4 illustrates the likelihood ratio scatter matrix (all supplementary materials are available in Online Supplementary Information). Twenty-four studies investigated the prognostic capability of diabetes in AIS. The meta-analysis demonstrated that the prognostic accuracy of diabetes for poor functional outcome at 90 days

Table 1. Clinical characteristics of studies included in the meta-analysis

Author	Year	Country	Study type	Cohort (number of patients)	Age (years ±SD)	Male (%)	Reperfusion	sICH criteria	Recanalization criteria
Ahmed et al.[29]	2010	more than 1	prospective	15,787	68.19 ±12.83	58.86	IVT	SITS-MOST	–
Bauza et al.[46]	2018	USA	retrospective	645	NR	51.78	IVT	–	–
Borggrefe et al.[26]	2018	Germany	retrospective	317	70 ±14.5	48.58	EVT	ECASS-II	–
Chen et al.[47]	2019	China	retrospective	160	63.2 ±12.2	67.5	EVT	–	–
Cucchiara et al.[48]	2009	more than 1	retrospective	965	68 ±13	56.99	IVT	SITS-MOST	–
Fang et al.[34]	2020	China	retrospective	1084	63.44 ±11.39	60.89	IVT	SITS-MOST	–
Filipov et al.[49]	2018	Germany	retrospective	527	72.22 ±14.07	50.66	IVT	SITS-MOST	–
Fuentes et al.[50]	2014	Spain	prospective	261	67.59 ±12.59	57.09	IVT	–	–
Kim et al.[51]	2019	South Korea	retrospective	125	68.1 ±13.5	55.2	EVT	–	–
Lansberg et al.[52]	2007	USA	retrospective	74	70.76 ±14.86	55.41	IVT	≥2-point change in NIHSS associated with any degree of hemorrhage on CT or MR	–
Mishra et al.[30]	2010	more than 1	retrospective	1585	NR	NR	IVT	–	–
Montalvo et al.[53]	2019	USA	retrospective	578	72.55 ±15.06	47.75	EVT	ECASS-III	–
Ngiam et al.[54]	2022	Singapore	retrospective	666	64.9 ±14.3	60.66	IVT	–	–
Nikneshan et al.[55]	2013	Canada	retrospective	1689	NR	NR	IVT	SITS-MOST	–
Nowak et al.[56]	2020	Poland	retrospective	291	66 ±15	50.86	EVT	–	–
Reiter et al.[42]	2014	Austria	retrospective	2158	matched analysis		IVT	NR	–
Ribo et al.[35]	2005	Spain	prospective	139	71 ±11.4	56.83	IVT	–	TCD ultrasound
Tang et al.[36]	2016	China	retrospective	419	67.12 ±13.08	63.25	IVT	NR	TIMI
Tsivgoulis et al.[32]	2019	more than 1	retrospective	54,206	70.13 ±13.21	54.60	IVT	SITS-MOST	–
Wang et al.[57]	2019	China	retrospective	403	67.01 ±31.88	66.25	IVT	–	–
Wnuk et al.[31]	2020	Poland	retrospective	181	66.15 ±9.5	51.38	EVT	–	mTICI
Xu et al.[58]	2017	China	retrospective	162	65.6 ±10.6	63.58	IVT	–	–
Yoo et al.[59]	2014	South Korea	retrospective	207	70.6 ±11.11	61.35	IVT	–	–
Zhang et al.[60]	2019	China	prospective	135	64.2 ±5.5	57.78	IVT	–	NR

SD – standard deviation; EVT – endovascular thrombectomy; IVT – intravenous thrombolysis; ST – systemic thrombolysis; mRS – modified Rankin Scale; sICH – symptomatic intracerebral hemorrhage; ECASS-II – the Second European-Australasian Acute Stroke Study; ECASS-III – the Third European Cooperative Acute Stroke Study; SITS-MOST – Safe Implementation of Thrombolysis in Stroke-Monitoring Study; NR – not reported; HT – hemorrhagic transformation; NIHSS – National Institutes of Health Stroke Scale; TIMI – Thrombolysis in Myocardial Infarction; TCD – transcranial Doppler; mTICI – modified Thrombolysis in Cerebral Infarction; CT – computed tomography; MR – magnetic resonance.

Table 2. Clinical outcomes of studies included in the meta-analysis

Author	Poor functional outcome at 90 days		Poor functional outcome at discharge		Mortality outcome at 90 days		sICH		HT		Poor recanalization	
	diabetes (n, %)		diabetes (n, %)		diabetes (n, %)		diabetes (n, %)		diabetes (n, %)		diabetes (n, %)	
	yes	no	yes	no	yes	no	yes	no	yes	no	yes	no
Ahmed et al.[29]	1335 (57.39)	4970 (44.7)	–	–	515 (21.81)	1467 (13)	69 (2.59)	89 (1.48)	–	–	–	–
Bauza et al.[46]	90 (55.21)	275 (58.64)	–	–	–	–	–	–	–	–	–	–
Borggrefe et al.[26]	33 (76.74)	151 (60.4)	–	–	13 (30.23)	54 (21.6)	5 (12.82)	10 (3.8)	–	–	–	–
Chen et al.[47]	17 (58.62)	72 (54.96)	–	–	–	–	–	–	–	–	–	–
Cucchiara et al.[48]	–	–	–	–	–	–	10 (5.18)	44 (5.7)	52 (23.53)	141 (18.95)	–	–
Fang et al.[34]	81 (42.41)	356 (39.87)	–	–	25 (13.09)	83 (9.29)	7 (3.66)	13 (1.46)	–	–	–	–
Filipov et al.[49]	–	–	120 (63.16)	170 (50.30)	–	–	11 (5.82)	5 (1.48)	42 (22.22)	50 (14.79)	–	–
Fuentes et al.[50]	–	–	22 (38.6)	57 (33.93)	–	–	–	–	8 (12.9)	16 (8.04)	–	–
Kim et al.[51]	27 (69.23)	48 (55.81)	–	–	–	–	–	–	–	–	–	–
Lansberg et al.[52]	–	–	–	–	–	–	3 (15)	4 (7.41)	–	–	–	–
Mishra et al.[30]	221 (64.62)	681 (54.79)	–	–	69 (20.18)	184 (14.8)	–	–	–	–	–	–
Montalvo et al.[53]	–	–	–	–	–	–	8 (5.93)	11 (2.48)	–	–	–	–
Ngiam et al.[54]	65 (51.59)	240 (44.44)	–	–	–	–	–	–	–	–	–	–
Nikneshan et al.[55]	–	–	252 (75.68)	934 (68.88)	–	–	25 (7.51)	92 (6.8)	42 (12.61)	169 (12.46)	–	–
Nowak et al.[56]	50 (62.5)	87 (41.23)	–	–	22 (27.5)	41 (19.43)	–	–	–	–	–	–
Reiter et al.[42]	–	–	691 (64.04)	658 (60.98)	–	–	53 (4.91)	38 (3.52)	–	–	–	–
Ribo et al.[35]	–	–	–	–	–	–	–	–	–	–	21 (72.41)	74 (67.27)
Tang et al.[36]	–	–	–	–	–		2 (2.04)	13 (4.05)	–	–	31 (91.18)	84 (75)
Tsivgoulis et al.[32]	5637 (51.72)	17,626 (40.7)	–	–	2608 (23.93)	6794 (15.69)	280 (2.57)	702 (1.62)	–	–	–	–
Wang et al.[57]	–	–	–	–	–	–	–	–	5 (10)	41 (11.61)	–	–
Wnuk et al.[31]	25 (59.52)	60 (43.17)	–	–	–	–	–	–	21 (50)	58 (41.73)	15 (35.71)	48 (34.53)
Xu et al.[58]	–	–	–	–	–	–	–	–	3 (7.69)	17 (13.82)	–	–
Yoo et al.[59]	29 (65.91)	101 (61.96)	–	–	9 (20.45)	24 (14.72)	–	–	23 (52.27)	62 (38.04)	–	–
Zhang et al.[60]	–	–	–	–	–	–	–	–	4 (5.71)	3 (4.62)	45 (64.29)	19 (29.23)

sICH – symptomatic intracerebral hemorrhage; HT – hemorrhagic transformation.

Table 3. Summary effects and heterogeneity obtained from the meta-analysis of the association of diabetes with clinical outcomes in acute ischemic stroke patients

Outcome	Reperfusion therapy	Effect measure	Summary Effects REDL	Heterogeneity¶		Heterogeneity variance estimates			
			OR (95% CI)	tests of overall effect	Cochran's Q	H	I^2≤*	p-value	τ^2≤†
Functional outcome at 90 days	overall	OR	1.487 [1.335; 1.656]	p < 0.0001 z = 7.225	22.05	1.416 (95% CI: [1.000; 1.916])	50.1% (95% CI: [0.0; 72.7])	0.024	0.0100
	IVT	OR	1.430 [1.270; 1.611]	p < 0.0001 z = 5.885	17.91	–	66.5%	0.006	–
	EVT	OR	1.941 [1.424; 2.646]	p < 0.0001 z = 4.199	2.21	–	0.0%	0.697	–
Functional outcome at discharge	overall (IVT)	OR	1.310 [1.091; 1.574]	p = 0.004 z = 2.896	4.43	1.215 (95% CI: [1.000; 2.163])	32.3% (95% CI: [0.0; 78.6%])	0.219	0.0114
Mortality at 90 days	overall	OR	1.709 [1.633; 1.788]	p < 0.0001 z = 23.111	4.24	0.840 (95% CI: [1.000; 1.552])	0.0% (95% CI: [0.0; 58.5%])	0.644	0.0000
	IVT	OR	1.713 [1.629; 1.801]	p < 0.0001 z = 20.934	4.11	–	2.7%	0.391	–
	EVT	OR	1.573 [0.994; 2.489]	p = 0.053 z = 1.933	0.00	–	0.0%	1.000	–
Recanalization	overall	OR	2.059 [0.963; 4.400]	p = 0.062 z = 1.863	9.13	1.774 (95% CI: [1.000; 2.729])	67.1% (95% CI: [0.0; 86.6%])	0.028	0.3938
	IVT	OR	2.693 [1.204; 6.027]	p = 0.016 z = 2.411	4.42	–	54.7%	0.110	–
	EVT	OR	1.053 [0.512; 2.167]	p = 0.888 z = 0.141	0.00	–	–	–	–
sICH	overall	OR	1.595 [1.301; 1.956]	p < 0.0001 z = 4.586	15.07	1.228 (95% CI: [1.000; 1.723])	33.7% (95% CI: [0.0; 66.3])	0.129	0.0310
	IVT	OR	1.524 [1.245; 1.866]	p < 0.0001 z = 4.079	11.98	–	33.2%	0.152	–
	EVT	OR	2.917 [1.421; 5.990]	p = 0.004 z = 2.917	0.30	–	0.0%	0.585	–
HT	overall	OR	1.276	p = 0.012 z = 2.517	6.67	0.918 (95% CI: [1.000; 1.480])	0.0% (95% CI: [0.0; 54.4])	0.564	0.0000
	IVT	OR	1.267	p = 0.019 z = 2.348	6.67	–	0.0%	0.464	–
	EVT	OR	1.397 [0.699; 2.791]	p = 0.344 z = 0.945	0.00	–	–	–	–

EVT – endovascular thrombectomy; IVT – intravenous thrombolysis; sICH – symptomatic intracerebral hemorrhage; HT – hemorrhagic transformation; REDL – DerSimonian and Laird random effects method; OR – odds ratio; Q – heterogeneity measures were calculated from the data with 95% confidence intervals (95% CIs), based on noncentral χ^2 (common effect) distribution for Cochran's Q test; H – relative excess in Cochran's Q over its degrees of freedom; I^2 – proportion of total variation in effect estimate due to between study heterogeneity (based on Cochran's Q test); τ^2 – between-study variance to test the comparisons of heterogeneity among subgroups; * values of I≤ are percentages; ¶ – heterogeneity measures were calculated from the data with 95% CIs based on gamma (random effects) distribution for Q; † – heterogeneity variance estimates (tau≤) were derived from the DerSimonian and Laird method.

was 56% (AUC: 0.56; 95% CI: [0.03; 0.98]). The pooled prognostic sensitivity of diabetes for poor functional outcome at 90 days was 59% (SENS: 0.59; 95% CI: [0.54; 0.64]; p < 0.0001). The test of heterogeneity revealed a considerable heterogeneity for diagnostic sensitivity (I^2 = 99.87) and specificity (I^2 = 99.93). The prognostic accuracy of diabetes for poor functional outcome at discharge was 56% (AUC: 0.56; 95% CI: [0.04; 0.98]). The pooled prognostic sensitivity of diabetes for poor functional outcome at discharge was 61% (SENS: 0.61; 95% CI: [0.47; 0.73]; p < 0.0001). The test of heterogeneity revealed a considerable heterogeneity for the diagnostic sensitivity (I^2 = 99.81) and specificity (I^2 = 99.45). The prognostic accuracy of diabetes for mortality at 90 days was 54% (AUC: 0.54; 95% CI [0.01; 0.99]). The pooled prognostic sensitivity of diabetes for mortality at 90 days was 23% (SENS: 0.23; 95% CI: [0.20; 0.26]; p < 0.0001). The test of heterogeneity revealed a considerable heterogeneity for the diagnostic sensitivity (I^2 = 94.13) and specificity (I^2 = 98.85). The prognostic accuracy of diabetes for poor recanalization was 61% (AUC: 0.61; 95% CI: [0.06; 0.98]). The pooled prognostic sensitivity of diabetes for poor recanalization was 70% (SENS: 0.7;

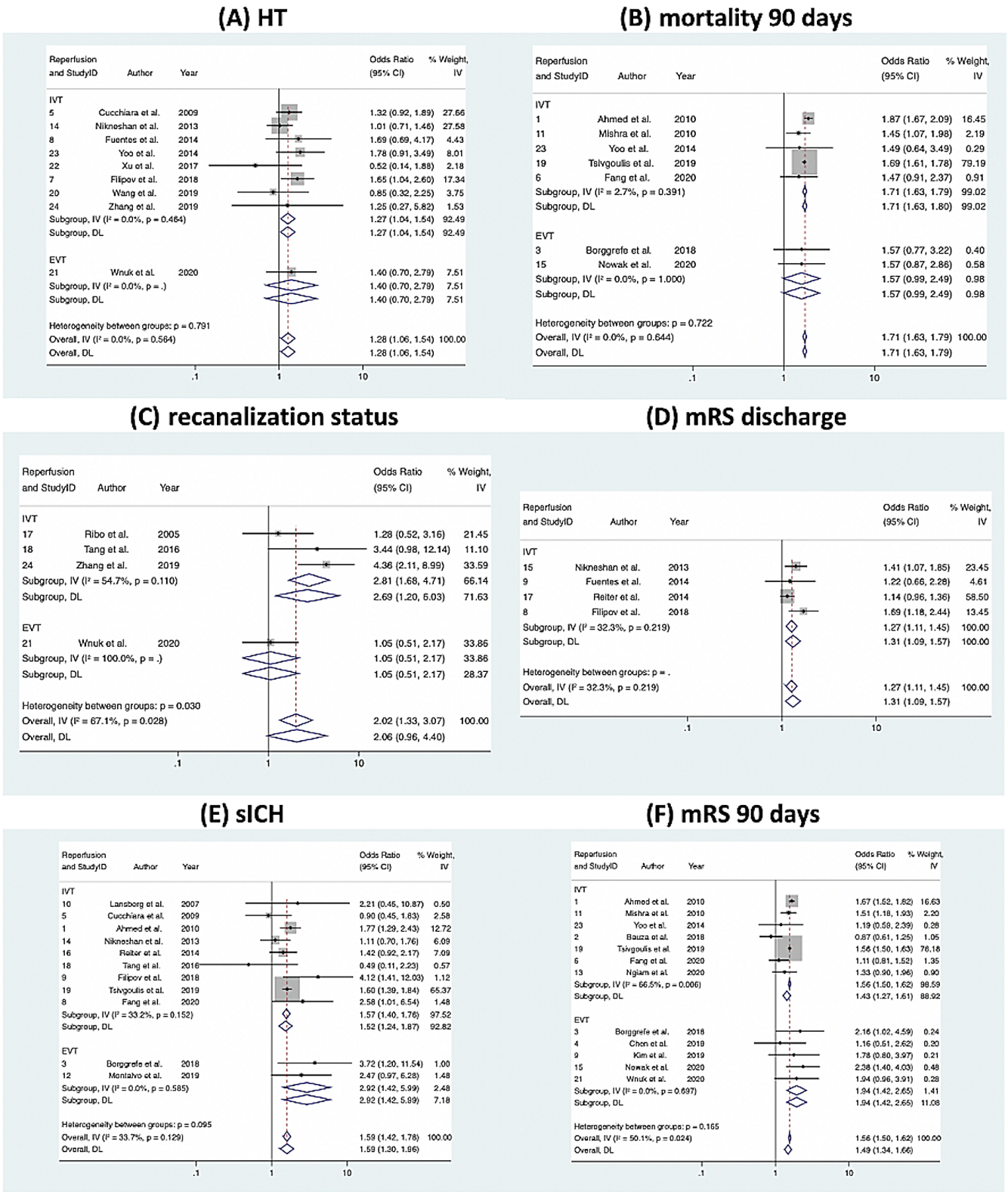

Fig. 2. Forest plot of estimated effect for the association of diabetes with: A. hemorrhagic transformation (HT); B. mortality at 90 days; C. recanalization status; D. functional outcome at discharge (mRS discharge); E. symptomatic intracerebral hemorrhage (sICH); and F. functional outcome at 90 days (mRS 90 days) in acute ischemic stroke patients receiving reperfusion therapy. Odds ratio of meta-analysis for the association of diabetes with poor functional outcome at 90 days, mortality at 90 days, symptomatic intracerebral hemorrhage, hemorrhagic transformation, recanalization status, and functional outcome at discharge. IVT – all patients received IVT; EVT – all patients received EVT.

mRS – modified Rankin scale score; IVT – intravenous thrombolysis; EVT – endovascular thrombectomy.

95% CI: [0.45; 0.86]; p < 0.0001). The test of heterogeneity revealed a considerable heterogeneity for diagnostic sensitivity (I^2 = 98.16) and specificity (I^2 = 96.72). The prognostic accuracy of diabetes for sICH was 42% (AUC: 0.42; 95% CI: [0.00; 1.00]). The pooled prognostic sensitivity of diabetes for sICH was 4% (SENS: 0.04; 95% CI: [0.03; 0.06]; p < 0.0001). The test of heterogeneity revealed considerable heterogeneity for diagnostic sensitivity (I^2 = 99.84) and specificity (I^2 = 99.99). The prognostic accuracy of diabetes for HT could not be determined.

Association of diabetes with the functional outcome at 90 days

Overall, 12 studies were included in the final meta-analysis of the association of diabetes with the poor functional outcome at 90 days, comprising a total of 72,874 patients. Poor functional outcome at 90 days was defined as mRS score of 3–6 in all studies. Diabetes was associated with significantly increased odds of poor functional outcome at 90 days (OR 1.487; 95% CI: [1.335; 1.656]; p < 0.0001) (Fig. 2F). Moderate to substantial heterogeneity was found between the studies (I^2 = 50.1%, p = 0.024). There was the evidence of publication bias, observed by visual inspection of the funnel plot (Supplementary Fig. 1), revealed by Egger's test (Supplementary Fig. 2; all supplementary materials are available in Online Supplementary Information). There was a significant association of diabetes with mRS at 90 days, observed in patients receiving IVT (OR 1.430; 95% CI: [1.270; 1.611]; p < 0.0001) and in patients receiving EVT (OR 1.941; 95% CI: [1.424; 2.646]; p < 0.0001).

Association of diabetes with mortality at 90 days

Seven studies were included in the final meta-analysis of the association of diabetes with mortality at 90 days, comprising a total of 71,312 patients. Diabetes was significantly associated with mortality at 90 days (OR 1.709; 95% CI: [1.633; 1.788]; p < 0.0001) (Fig. 2B). A low heterogeneity was found between the studies (I^2 = 0.0%, p = 0.644). There was the evidence of publication bias, observed by visual inspection of the funnel plot (Supplementary Fig. 1) and revealed by Egger's test (Supplementary Fig. 2; all supplementary materials are available in Online Supplementary Information). A significant association of diabetes with mortality at 90 days was observed in patients receiving IVT (OR 1.713; 95% CI: [1.629; 1.801]; p < 0.0001). No significant association of diabetes with mortality at 90 days was observed in patients receiving EVT (OR 1.573; 95% CI: [0.994; 2.489]; p = 0.0532) (Fig. 2B).

Association of diabetes with sICH

Overall, 11 studies were included in the final meta-analysis of the association of diabetes with sICH, comprising a total of 70,677 patients. The sICH was defined by SITS-MOST[21] criteria in 6 studies, ECASS-II[22] criteria in 1 study, National Institute of Neurological Disorders and Stroke (NINDS) criteria in 1 study, ECASS-III[23] criteria in 1 study, as ≥2 point change in National Institutes of Health Stroke Scale (NIHSS) score associated with any degree of hemorrhage on computed tomography (CT) or magnetic resonance (MR) in 1 study, and not defined in 2 studies. Overall, diabetes was significantly associated with an increased sICH rate (OR 1.595; 95% CI: [1.301; 1.956]; p < 0.0001) (Fig. 2E). A low to moderate heterogeneity was found between the studies (I^2 = 33.7%, p = 0.129). Some evidence of publication bias was observed by the visual inspection of the funnel plot (Supplementary Fig. 1) and by Egger's test (Supplementary Fig. 2; all supplementary materials are available in Online Supplementary Information). A significant association between diabetes and the odds of sICH was observed in patients receiving IVT (OR 1.524; 95% CI: [1.245; 1.866]; p < 0.0001) and those receiving EVT (OR 2.917; 95% CI: [1.421; 5.99]; p = 0.0035) (Fig. 2E).

Association of diabetes with HT

Nine studies were included in the final meta-analysis of the association of diabetes with HT, comprising a total of 4530 patients. Overall, diabetes was associated with increased odds of HT (OR 1.276; 95% CI: [1.055; 1.543]; p = 0.0118) (Fig. 2A). A low heterogeneity was found between the studies (I^2 = 0.0%, p = 0.564). There was the evidence of publication bias, observed by a visual inspection of the funnel plot (Supplementary Fig. 1), and revealed by Egger's test (Supplementary Fig. 2; all supplementary materials are available in Online Supplementary Information). There was also a significant association of diabetes with HT in patients specifically receiving IVT (OR 1.267; 95% CI: [1.040; 1.543]; p = 0.0188) (Fig. 2A).

Association of diabetes with recanalization status

The meta-analysis of the association of diabetes with recanalization status included 4 studies encompassing 601 patients. A poor recanalization outcome was defined as a Thrombolysis in Myocardial Infarction (TIMI) score <3 in 1 study, a modified Thrombolysis in Cerebral Infarction (mTICI) score <2b in 1 study and incomplete recanalization on transcranial Doppler ultrasound in 1 study, while it was not defined in 1 study. Although diabetes was associated with increased odds of incomplete recanalization status, the association failed to reach statistical significance (OR 2.059; 95% CI: [0.963; 4.400]; p = 0.0624) (Fig. 2C). A moderate to substantial heterogeneity was reported (I^2 = 67.1%, p = 0.028). There was no evidence of publication bias, observed by a visual inspection of the funnel plot (Supplementary Fig. 1) and revealed by Egger's test (Supplementary Fig. 2; all supplementary materials are available

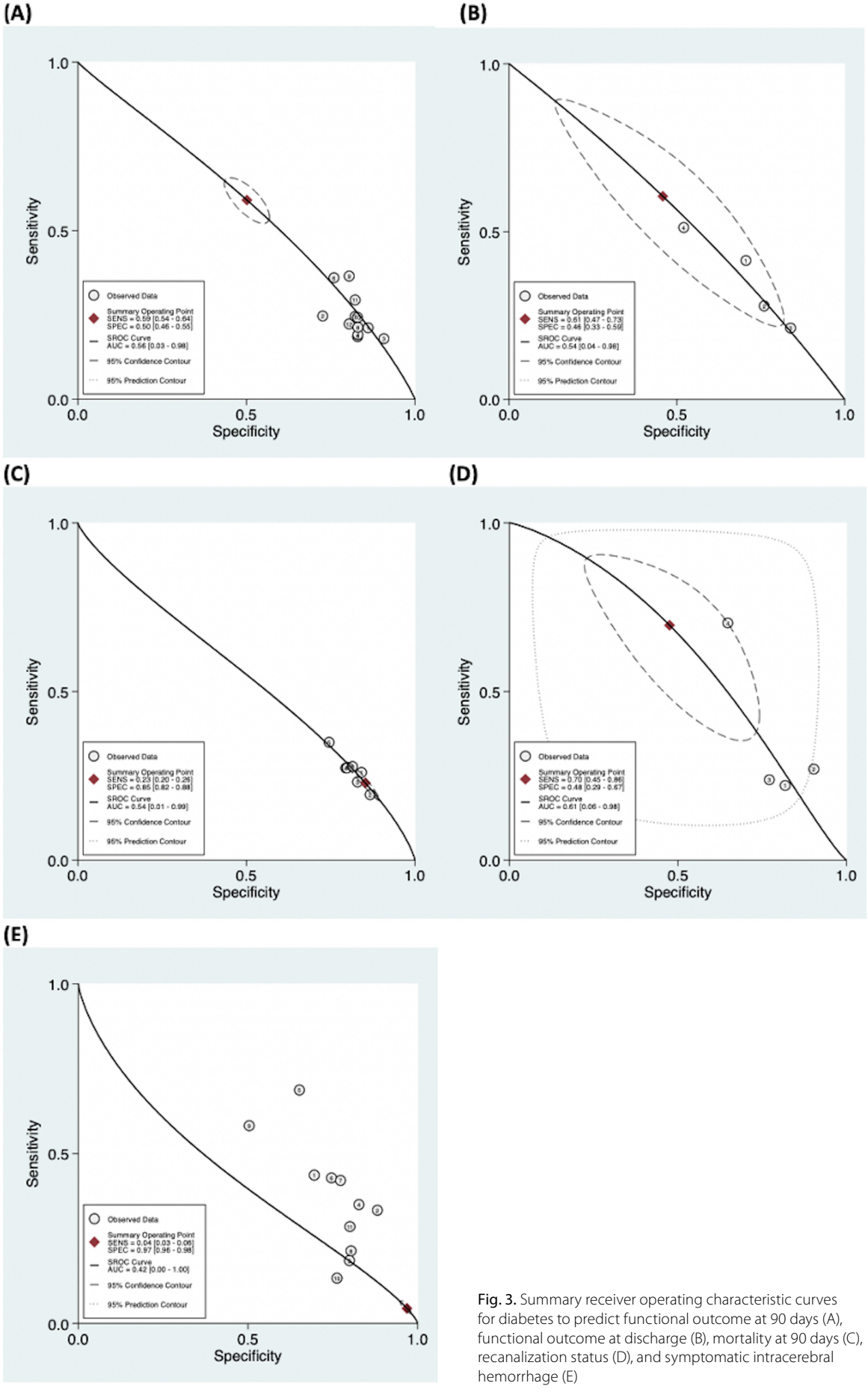

Fig. 3. Summary receiver operating characteristic curves for diabetes to predict functional outcome at 90 days (A), functional outcome at discharge (B), mortality at 90 days (C), recanalization status (D), and symptomatic intracerebral hemorrhage (E)

in Online Supplementary Information). There was, however, a significant association of diabetes with incomplete recanalization status in IVT patients (OR 2.693; 95% CI: [1.204; 6.027]; p = 0.0159).

Association of diabetes with the functional outcome at discharge

Four studies were included in the meta-analysis of the association of diabetes with poor functional outcome at discharge, defined as mRS score of 3–6 at discharge. A total of 4600 patients were included, and patients in all included studies received IVT. Diabetes was associated with a significantly increased odds of poor functional outcome at discharge (OR 1.310; 95% CI: [1.091; 1.574]; p = 0.0037) (Fig. 2D). Low to moderate heterogeneity was found (I^2 = 32.3%, p = 0.219). There was the evidence of publication bias, observed by visual inspection of the funnel plot (Supplementary Fig. 1) and revealed by Egger's test (Supplementary Fig. 2; all supplementary materials are available in Online Supplementary Information).

Discussion

The results of this meta-analysis demonstrate that diabetes is associated with increased mortality and poor clinical and safety outcomes in AIS patients receiving reperfusion therapy. Specifically, diabetes was associated with poor functional outcome at discharge and at 90 days, as well as mortality at 90 days. The IVT and EVT subgroup analysis revealed similar outcomes; however, the association of diabetes with mortality at 90 days in EVT patients was not significant. With regard to postprocedural outcomes, AIS patients with pre-existing diabetes were associated with significantly increased odds of any HT or sICH after the reperfusion therapy. In particular, there was a strong association between diabetes and sICH in IVT patients. Although patients with diabetes were at increased odds of incomplete recanalization after the reperfusion therapy, the association failed to reach statistical significance overall. However, the association of diabetes with incomplete recanalization was significant for the IVT subgroup.

Identifying biomarkers or phenotypes associated with poor or better clinical profiles in AIS patients receiving reperfusion therapy is important in order to stratify patients for an optimal therapy.[10] Furthermore, given the rising prevalence of diabetes in the increasingly developing world, the proportion of AIS patients with diabetes is also expected to increase, warranting public health and clinical attention.[24] Within the AIS population with diabetes, patients with acute hyperglycemia are at an even increased risk of poor outcome profiles, as acute hyperglycemia is associated with an increased risk of infarct growth – by potentially impairing the vulnerability of penumbra.[25] Therefore, patients with diabetes, especially those with acute hyperglycemia, need urgent attention and rapid reperfusion treatment. Previous studies have indicated longer times to reperfusion in diabetes patients, owing to the additional need for medical care for hyperglycemia or diabetes management, prior to the reperfusion therapy.[26,27] On a systemic level, this warrants establishing specialized pathways to identify AIS patients with a high risk of poor outcomes.[9,28]

Current evidence on functional outcome at 90 days for patients with diabetes who have undergone reperfusion therapy is mixed.[5,26,29–31] Most of the studies included in this meta-analysis did not individually find a significant relationship between diabetes and the odds of poor functional outcome. Tsivgoulis et al.,[32] with the largest cohort of any study (n = 54,206), did find a significant relationship. However, the study was of retrospective design. De Silva et al.,[33] Fang et al.[34] and Tsivgoulis et al.[32] all found a significant relationship between the glucose level at admission and a poor functional outcome, in patients with or without diabetes, indicating that a poor functional outcome may be associated more with acute hyperglycemia seen in AIS patients. Our meta-analysis demonstrated a significant association between diabetes and a poor functional outcome at discharge and at 3 months. It also found a significant association between diabetes and increased 90 days mortality after the reperfusion therapy. A further investigation is needed in order to determine whether factors such as acute hyperglycemia and prior stroke play a role in these findings. Our meta-analysis found a significant association, although in a limited sample size drawn from 4 studies, between diabetes and unsuccessful recanalization, which contrasted with the individual findings of most of the included studies.[14,31,35–37]

With regard to safety outcomes, our meta-analysis revealed significantly increased odds of sICH and HT for AIS patients with diabetes who have undergone reperfusion therapy, compared to those without diabetes. This corroborates previous meta-analyses stating that diabetes and tPA independently increase the risk of hemorrhagic events after a stroke.[14,38] This meta-analysis considers the impact of diabetes across all reperfusion therapies. From a pathophysiological perspective, rodent models have demonstrated that increased MMP-9, the receptor for advanced glycation end products (RAGE) and vascular endothelial growth factor (VEGF) in diabetic mice are associated with increased blood–brain barrier (BBB) leakage, hemorrhage and impaired functional outcome.[37,39] The IVT may further exacerbate BBB leakage through BBB disruption.[40] Factors such as delayed onset-to-reperfusion time and leukoaraiosis have also been implicated.[3,41] Regardless, studies have shown that reperfusion therapy is safe for patients with diabetes and leads to better outcomes compared to patients who did not receive reperfusion therapy.[30,42]

During the current coronavirus disease 2019 (COVID-19) pandemic, an increasing attention is being paid to the disproportionate burden on patients with

pre-existing diabetes.[43–45] Furthermore, studies also indicate that patients with diabetes may be at an increased risk of COVID-19 infection.[44] This highlights the need for comprehensive and tailored management of patients with diabetes during the pandemic and beyond,[43] as well as in stroke patients with pre-existing diabetes who are at risk of poor outcomes after AIS.[46–60]

Limitations

This study has several limitations. Most studies included in the meta-analysis were retrospective, and thus inherently limited in their design. This also resulted in most of the included studies relying on a history of diabetes diagnosis or diabetes treatment as criteria for inclusion in the treatment group. This means that there may be some patients in the control group with undiagnosed diabetes. The inclusion of case-controlled studies may cause spectrum bias or random error. However, most of the studies reported that all consecutive acute ischemic stroke patients receiving reperfusion therapy were included; this may minimize the selection bias. Furthermore, certain parameters such as diabetic severity, duration and type were either minimally reported or not reported at all. Due to its large sample size, the study by Tsivgoulis et al.[32] had a disproportionate effect on the overall results. Supplementary Fig. 5 (Online Supplementary Information) displays the results with the exclusion of that study. The outcomes of poor recanalization and functional outcome at discharge had relatively small cohorts and were therefore not highly powered. Last, not all studies clearly defined the number of patients who received both thrombolysis and thrombectomy. Findings should be interpreted on methodological design and the study population. However, given the fact that we performed a random effects model, some of these variabilities and heterogeneities will be accounted for.

Conclusions

Diabetes is an important clinical consideration in AIS patients receiving reperfusion therapy. Our meta-analysis demonstrates that diabetes is associated with poor outcomes such as poor functional outcome, mortality, and poor safety outcomes, including sICH and HT. These results are mostly consistent across reperfusion treatment subgroups.

Data availability statement

The original contributions presented in the study are included in the article Online Supplementary Information; further inquiries can be directed to the corresponding author. The Online Supplementary Information is available online at https://doi.org/10.5281/zenodo.5930131.

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